REMARKS

Reconsideration of the above referenced application is respectfully requested. Upon entry of the foregoing amendment, Claims 72-87 and 96-134 are presently pending. Claims 72-87 have been withdrawn. Claims 88-95 have been cancelled herein without prejudice or disclaimer. Applicants reserve the right to pursue the subject matter of the cancelled claims in one or more continuation or divisional application. New claims 96-135 have been added. Basis for the claims may be found throughout the specification and in the claims as originally filed. No new matter has been introduced and entry of this amendment is respectfully requested.

Support For The New Claims

The claims indicate that the number 1 carbon of the second (right-hand) monosaccharide can be in the beta (equatorial or below the plane) or in the alpha (axial or above the plane), position. Support for the alternative positions of the number 1 carbon of the second (right-hand) monosaccharide may be found in the claims as filed and in the specification at least on page 40, as reflected in the current claims.

Support for the claimed compositions is found in Table 7 and in the claims as filed. Support the claim features related to the % by weight of the transduction enhancing agent in the pretreatment composition, the volume of oncolytic virus composition administered to the bladder by instillation, the time of instillation, the number of viral particles, and pretreatment compositions which further comprise an oxidizing agent such as hypochlorous acid, hydrogen peroxide or peroxyacetic acid may be found in Claims 72-85 and in Claims 72-85, as filed.

Patentability Over The Art

Applicants respectfully submit that the presently claims are not anticipated by the references cited in U.S. Application Serial No. 10/327,869, upon which the instant application claims priority. The references cited as priori art in U.S. Application Serial No. 10/327,869 are addressed individually and in detail below.

Mizamura et al. was cited in the August 31, 2005 Office Action in U.S. Application Serial No. 10/327,869, as allegedly disclosing a composition comprising purified Newcastle disease virus (characterized as an oncolytic virus) in 4% octyl-beta-D-glucopyranoside, a monosaccharide.

Anticipation under 35 U.S.C. § 102 requires that the reference "must teach every aspect of the claimed invention either explicitly or impliedly. Any feature not directly taught must be inherently present." (MPEP §706.02). "A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987).

Mizamura et al. does not disclose an oncolytic adenovirus composition comprising a disaccharide, having a lipophilic substituent, which exhibits preferential expression in the bladder epithelium, as presently claimed.

Zhang et al. was cited in the August 31, 2005 Office Action in U.S. Application Serial No. 10/327,869, as allegedly teaching that adenovirus CG8840 was a urothelium-specific adenovirus variant that eliminates bladder tumors when administered in combination with docetaxel. The Office Action further states that Zhang et al. did not teach administration to the luminal surface of the bladder or the use of a transduction enhancing mono-, di-, or poly-saccharides having a lipophilic substituent. Conner et al. was also cited in the August 31, 2005

Office Action in U.S. Application Serial No. 10/327,869, as allegedly teaching that adenoviral infection of the urothelium was improved when adenovirus was delivered to the urothelium with octyl-beta-D-glucopyranoside (table 1, page 42). The Examiner acknowledged that Conner et al. did not teach sequential addition of octyl-beta-D-glucopyranoside followed by adenovirus, but instead added them simultaneously and that the process of Conner et al. differs from the current claims with respect to the wash step and the amount of virus. However, the Examiner referred to MPEP 2144.04 (IV)(C) in taking the position that selection of any order of performing process steps is prima facie obvious in the absence of new or unexpected results and that variables such as volume of virus solution and number of viral particles are not sufficient to support patentability unless there is evidence to support the fact that such concentration or temperature is critical, alleging that such variables can be optimized by routine experimentation.

The Office Action further states that it would have been obvious to one of ordinary skill in the art at the time of the invention to modify the method of Zhang et al. by applying adenovirus to the luminal surface of a bladder, as taught by Conner et al., in order to treat bladder cancer.

Conner et al. was cited as allegedly teaching that adenoviral infection of the urothelium was improved when adenovirus was delivered to the urothelium with octyl-beta-D-glucopyranoside. In contrast, the present invention relies on the use of a disaccharide, having a lipophilic substituent to enhance adenoviral transduction of the bladder epithelium. As indicated in the specification of the priority application for the instant case (U.S. Application Serial No. 10/327,869; page 41, lines 4-5), n-dodecyl-beta-D-glucopyranoside showed little or no enhancement of bladder transduction.

To establish a *prima facie* case of obviousness the prior art reference (or references when combined) must teach or suggest all of the claim limitations. *In re Vaeck*, 20 USPQ2d 1438 (Fed. Cir. 1991) and MPEP § 2142. Moreover, when applying 35 U.S.C. § 103, the following tenets of patent law must be adhered to: (A) The claimed invention must be considered as a whole; (B) The references must be considered as a whole and must suggest the desirability and thus the obviousness of making the combination; (C) The references must be viewed without the benefit of impermissible hindsight vision afforded by the claimed invention; and (D) Reasonable expectation of success is the standard with which obviousness is determined. *Hodosh v. Block Drug Co., Inc.*, 229 USPQ 182, 187 n.5 (Fed. Cir. 1986).

For the reasons set forth above not only does the combination of Zhang et al. and Conner et al., not teach or suggest an oncolytic adenovirus composition comprising a disaccharide, having a lipophilic substituent which exhibits preferential expression in the bladder epithelium, as presently claimed, the use of octyl-beta-D-glucopyranoside as taught by Conner et al. is inconsistent with the teachings of the specification of the instant application as stated above. The instant application teaches that adenoviral infection of the urothelium was improved when adenovirus was delivered to the urothelium with disaccharide transduction enhancing agents, but not when treated with a monosaccharide as taught by Conner et al. Hence one of skill in the art, relying on the cited references would not have a reasonable expectation of success in practicing the present invention and the standard for obviousness has not been met.

Furthermore, the combined references do not teach or suggest all of the claim limitations and the combination of Zhang et al. and Conner et al. does not render the current claims obvious.

Watanabe et al. was cited in the August 31, 2005 Office Action in U.S. Application Serial No. 10/327,869 as allegedly teaching treatment of bladder cancer with replication deficient

adenovirus carrying a suicide gene in an orthotopic mouse model of human bladder-cancer. The Examiner acknowledged that Watanabe et al. did not teach an oncolytic virus or the use of a transduction enhancing agent.

Conner et al. is summarized above. Conner et al. was cited as allegedly teaching that adenoviral infection of the urothelium was improved when adenovirus was delivered to the urothelium with octyl-beta-D-glucopyranoside. In contrast, the present invention relies on the use of a disaccharide, having a lipophilic substituent to enhance adenoviral transduction of the bladder epithelium. As indicated on page 41, lines 4-5 of the priority application for the instant case (U.S. Application Serial No. 10/327,869), n-dodecyl-beta-D-glucopyranoside showed little or no enhancement of bladder transduction.

On page 9 of the August 31, 2005 Office Action in U.S. Application Serial No. 10/327,869, Mullen was cited as allegedly teaching that oncolytic viruses expressing therapeutic transgenes offered a distinct advantage over analogous replication deficient gene therapy vectors because the virus amplifies itself through several rounds of replication resulting in an increase in transgene expression.

The Office Action further states that it would have been obvious to one of ordinary skill in the art at the time of the invention to modify the method of Watanabe et al. by treating bladders with octyl-beta-D-glucopyranoside and to substitute replication competent adenovirus for replication deficient adenovirus in order to take advantage of an amplified antitumor effect due to viral replication. As set forth above, the Examiner did not find variables such as volume of virus solution and number of viral particles sufficient to support patentability unless there is evidence to support the fact that such concentration or temperature is critical, alleging that such variables can be optimized by routine experimentation.

For the reasons set forth above not only does the combination of Watanabe et al., Zhang et al. and Conner et al., not teach or suggest an oncolytic adenovirus composition comprising a disaccharide, having a lipophilic substituent which exhibits preferential expression in the bladder epithelium, as presently claimed, the use of octyl-beta-D-glucopyranoside as taught by Conner et al. is inconsistent with the teachings of the specification of the instant application, as stated above. It follows that one of skill in the art relying on the teachings of Conner et al. would expect a monosaccharide such as octyl-beta-D-glucopyranoside to enhance transduction of an oncolytic adenovirus composition. The specification of the instant application teaches that this is in fact not the case. The instant application teaches that adenoviral infection of the urothelium was improved when adenovirus was delivered to the urothelium with disaccharide transduction enhancing agents, but not when treated with a monosaccharide as taught by Conner et al.

Accordingly, the combined references do not teach or suggest all of the claim limitations and the claims are therefore not obvious in view of the combination of cited art.

On page 11 of the August 31, 2005 Office Action in U.S. Application Serial No. 10/327,869, it is stated that the teachings of Watanabe et al., Conner et al. and Mullen et al. can be combined to render obvious a method of treating superficial bladder cancer by treating the luminal surface with octyl-beta-D-glucopyranoside and exposing the treated surface to an oncolytic adenovirus and that it was known that the urothelial gag layer was an impediment to luminal administration of adenovirus vectors and that detergents provide a means to improve transduction efficiency. The Examiner acknowledged that none of Watanabe et al., Conner et al. and Mullen et al. teach a disaccharide comprising a lipophilic substituents and relied on Boer et al. as allegedly teaching dodecyl-beta-D-maltopyranoside is a detergent with performance

characteristics similar to octyl-beta-D-glucopyranoside for solublizing vasopressin receptors from membranes.

The Office Action further states that it would have been obvious to one of ordinary skill in the art at the time of the invention to use dodecyl-beta-D-maltopyranoside as a detergent to improve adenoviral transduction of the bladder in the invention of Watanabe et al., as modified by Conner et al. and Mullen et al.

For the reasons set forth above, the combination of Watanabe et al., Zhang et al. and Conner et al., does not teach or suggest an oncolytic adenovirus composition comprising a disaccharide, having a lipophilic substituent which exhibits preferential expression in the bladder epithelium, as presently claimed. Boer et al. does not make up for this deficiency. One of skill in the art would appreciate that the performance characteristics of octyl-beta-D-glucopyranoside relative to dodecyl-beta-D-maltopyranoside in solublizing vasopressin receptors from membranes is not suggestive of the relative ability of the two compounds to enhance transduction of the bladder epithelium by an oncolytic adenovirus, in particular in light of data in the specification of the priority application for the instant case (U.S. Application Serial No. 10/327,869; page 41, lines 4-5) which demonstrates that the relative ability of monosaccharide versus disaccharides to enhance transduction of the bladder epithelium by an oncolytic adenovirus, is not the same.

Accordingly, the combined references do not teach or suggest all of the claim limitations and the claims are not obvious in view of the cited art.

On page 14 of the August 31, 2005 Office Action in U.S. Application Serial No. 10/327,869, it is stated that the teachings of Watanabe et al., Conner et al. and Mullen et al. can be combined to render obvious a method of treating superficial bladder cancer by treating the

luminal surface with octyl-beta-D-glucopyranoside and exposing the treated surface to an oncolytic adenovirus and that it was known that the urothelial gag layer was an impediment to luminal administration of adenovirus vectors and that detergents provide a means to improve transduction efficiency. The Examiner acknowledged that none of Watanabe et al., Conner et al. and Mullen et al. teach a disaccharide comprising a lipophilic substituents and relied on Sedzik et al. as allegedly teaching dodecyl-beta-D-maltopyranoside, decyl-beta-D-maltopyranoside, cyclohexyl pentyl-beta-D-maltoside, cyclohexyl hexyl-beta-D-maltoside, octyl-beta-D-thioglucopyranoside and heptyl-beta-D-thioglucopyranoside as detergents with performance characteristics similar to octyl-beta-D-glucopyranoside for solublizing PNS myelin membrane proteins.

The Office Action further states that it would have been obvious to one of ordinary skill in the art at the time of the invention to use the detergents recited in Sedzik et al. to improve adenoviral transduction of the bladder in the invention of Watanabe et al., as modified by Conner et al. and Mullen et al.

For the reasons set forth above, the combination of Watanabe et al., Zhang et al. and Conner et al., does not teach or suggest an oncolytic adenovirus composition comprising a disaccharide, having a lipophilic substituent which exhibits preferential expression in the bladder epithelium, as presently claimed. Sedzik et al. does not make up for this deficiency. One of skill in the art would appreciate that the performance characteristics of dodecyl-beta-D-maltopyranoside, decyl-beta-D-maltopyranoside, cyclohexyl pentyl-beta-D-maltoside, cyclohexyl hexyl-beta-D-maltoside, octyl-beta-D-thioglucopyranoside and heptyl-beta-D-thioglucopyranoside as detergents for solublizing PNS myelin membrane proteins is not suggestive of the relative ability of various compounds to enhance transduction of the bladder

epithelium by an oncolytic adenovirus, in particular in light of data in the specification of the priority application for the instant case (U.S. Application Serial No. 10/327,869; page 41, lines 4-5) which states that n-dodecyl-beta-D-glucopyranoside showed little or no enhancement of bladder transduction, while treatment of the bladder epithelium with dodecyl-beta-D-maltoside and 6-cyclohexyl hexyl-beta-D-maltoside resulted in a high level of transduction (page 37, line 24 through page 38, line 1).

Accordingly, the combined references do not teach or suggest all of the claim limitations and the claims are therefore not obvious in view of the combination of cited art.

On page 18 of the August 31, 2005 Office Action in U.S. Application Serial No. 10/327,869, it is stated that the teachings of Watanabe et al., Conner et al. and Mullen et al. can be combined to render obvious a method of treating superficial bladder cancer by treating the luminal surface with octyl-beta-D-glucopyranoside and exposing the treated surface to an oncolytic adenovirus and that it was known that the urothelial gag layer was an impediment to luminal administration of adenovirus vectors and that detergents provide a means to improve transduction efficiency. The Examiner acknowledges that none of Watanabe et al., Conner et al. and Mullen et al. teach a disaccharide comprising an alkanoic acid residue or sucrose residue and relied on Amiel et al. as allegedly teaching that a variety of detergents such as sucrose monolaureate and dodecyl maltoside, as well as TWEEN-20 and TWEEN-80 could be used as alternatives to octyl-beta-D-glucopyranoside, including sucrose monolaurate and dodecyl maltoside.

The Office Action further states that it would have been obvious to one of ordinary skill in the art at the time of the invention to use sucrose monolaurate or lauryl maltoside (i.e. dodecyl-beta-D-maltoside) as a detergent to improve adenoviral transduction of the bladder in the invention of Watanabe et al., as modified by Conner et al. and Mullen et al.

For the reasons set forth above, the combination of Watanabe et al., Zhang et al. and Conner et al., does not teach or suggest an oncolytic adenovirus composition comprising a disaccharide, having a lipophilic substituent which exhibits preferential expression in the bladder epithelium, as presently claimed. Amiel et al. does not make up for this deficiency. One of skill in the art would appreciate that the performance characteristics of monolaureate and dodecyl maltoside, as well as TWEEN-20 and TWEEN-80 could be used as alternatives to octyl-beta-D-glucopyranoside as detergents is not suggestive of the relative ability of various compounds to enhance transduction of the bladder epithelium by an oncolytic adenovirus, in particular in light of data in the specification of the priority application for the instant case (U.S. Application Serial No. 10/327,869; page 41, lines 4-5) which states that n-dodecyl-beta-D-glucopyranoside showed little or no enhancement of bladder transduction, while treatment of the bladder epithelium with dodecyl-beta-D-maltoside and 6-cyclohexyl hexyl-beta-D-maltoside resulted in a high level of transduction (page 37, line 24 through page 38, line 1).

Accordingly, the combined references do not teach or suggest all of the claim limitations and the claims are not obvious in view of the cited art.

On page 21-22 of the August 31, 2005 Office Action in U.S. Application Serial No. 10/327,869, it is stated that the teachings of Watanabe et al., Conner et al. and Mullen et al. can be combined to render obvious a method of treating superficial bladder cancer by treating the luminal surface with octyl-beta-D-glucopyranoside and exposing the treated surface to an oncolytic adenovirus. The Examiner acknowledges that none of Watanabe et al., Conner et al. and Mullen et al. teach a composition comprising an oncolytic virus and a chemotherapeutic agent and relied on Kirn et al. as allegedly teaching that oncolytic viruses sensitized tumor cells to chemotherapeutic agents.

The Office Action further states that it would have been obvious to one of ordinary skill in the art at the time of the invention to combine the methods of Watanabe et al., as modified by Conner et al. and Mullen et al. with a chemotherapeutic agent because Kirn et al. allegedly teaches that oncolytic viruses sensitized tumor cells to chemotherapeutic agents. The Office Action also stated that the intravesicular administration of chemotherapeutic agents is obvious.

For the reasons set forth above not only does the combination of Watanabe et al., Zhang et al. and Conner et al., not teach or suggest an oncolytic adenovirus composition comprising a disaccharide, having a lipophilic substituent which exhibits preferential expression in the bladder epithelium, as presently claimed, the use of octyl-beta-D-glucopyranoside as taught by Conner et al. is inconsistent with the teachings of the specification of the instant application, as stated above. The teachings of Kirn et al. relative to sensitization of tumor cells to chemotherapeutic agents do not make up for the lack of teaching by Watanabe et al., Zhang et al. and Conner et al.

Accordingly, the combined references do not teach or suggest all of the claim limitations and the claims are therefore not obvious in view of the combination of cited art.

On page 23 of the August 31, 2005 Office Action in U.S. Application Serial No. 10/327,869, it is stated that the teachings of Watanabe et al., Conner et al. and Mullen et al. can be combined to render obvious a method of treating superficial bladder cancer by treating the luminal surface with octyl-beta-D-glucopyranoside and exposing the treated surface to an oncolytic adenovirus. The Examiner acknowledged that none of Watanabe et al., Conner et al. and Mullen et al. teach a composition comprising an oncolytic virus and a chemotherapeutic agent and relied on Kirn et al. as allegedly teaching that oncolytic viruses sensitized tumor cells to chemotherapeutic agents and Rangel et al. as suggesting the use of Taxotere (docetaxel) as clinically useful for intravesicular use in bladder cancer treatment.

On page 23 of the August 31, 2005 Office Action in U.S. Application Serial No. 10/327,869, it is stated that it would have been obvious to one of ordinary skill in the art at the time of the invention to combine the method of Watanabeet al., as modified by Conner et al. and Mullen et al. with a chemotherapeutic agent because Kirn et al. allegedly teaches that oncolytic viruses sensitized tumor cells to chemotherapeutic agents and Rangel et al. suggested the use of Taxotere (docetaxel) as clinically useful for intravesicular use in bladder cancer treatment.

For the reasons set forth above not only does the combination of Watanabe et al., Zhang et al. and Conner et al., not teach or suggest an oncolytic adenovirus composition comprising a disaccharide, having a lipophilic substituent which exhibits preferential expression in the bladder epithelium, as presently claimed, the use of octyl-beta-D-glucopyranoside as taught by Conner et al. is inconsistent with the teachings of the specification of the instant application, as stated above. The teachings of Kirn et al. relative to oncolytic virus sensitization of tumor cells and Rangel et al. regarding the use of Taxotere (docetaxel) do not make up for the lack of teaching by Watanabe et al., Zhang et al. and Conner et al.

Accordingly, the combined references do not teach or suggest all of the claim limitations and the claims are therefore not obvious in view of the combination of cited art.

On page 24 of the August 31, 2005 Office Action in U.S. Application Serial No. 10/327,869, it is stated that it would have been obvious to one of ordinary skill in the art at the time of the invention to include hydrogen peroxide in the method of Watanabe et al., as modified by Conner et al., Mullen et al. and Kirn et al.

For the reasons set forth above not only does the combination of Watanabe et al., Zhang et al. and Conner et al., not teach or suggest an oncolytic adenovirus composition comprising a disaccharide, having a lipophilic substituent which exhibits preferential expression in the bladder

epithelium, as presently claimed, the use of octyl-beta-D-glucopyranoside as taught by Conner et al. is inconsistent with the teachings of the specification of the instant application, as stated above. The teachings of Kirn relative to oncolytic virus sensitization of tumor cells and Loughlin regarding the use of hydrogen peroxide as enhancing the efficacy of doxorubicin, do not make up for the lack of teaching by Watanabe et al., Zhang and Conner et al.

Accordingly, the combined references do not teach or suggest all of the claim limitations and the claims are therefore not obvious in view of the combination of cited art.

Conclusion

In light of the above, Applicants submit that this application is now in condition for allowance and therefore request favorable consideration. If any issues remain which the Examiner feels may be best resolved through a personal or telephonic interview, the Examiner is respectfully requested to contact Applicants' counsel, Linda R. Judge at (415) 836-2586.

Respectfully submitted,

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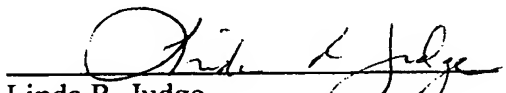

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